

REMARKS

Rejection of Claims and Traversal Thereof

In the July 5, 2005 Office Action,

claims 1-20 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-104 of U.S. Patent No. 6,713,452;

claims 19-20 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of U.S. Patent No. 6,835,802 in view of Lee, et al. (U.S. Patent No. 6,506,730, hereinafter Lee '730);

claims 1-6 and 8-18 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-130 of U.S. Patent No. 6,770,625;

claims 15-17 were rejected under 35 U.S.C. §103(a) as being obvious over EP 0 511 903 in view of Delgado et al (U.S. Patent No. 5,349,052, hereinafter Delgado '052) and WO 97/14740;

claims 15-17 were rejected under 35 U.S.C. §103(a) as being obvious over EP 0 511 903 in view of Delgado '052 and WO 97/14740 and in further view of the Harris et al article (*J. Macromol., Sci.*, Vol C25, pp 325-373, hereinafter Harris);

claims 15-18 were rejected under 35 U.S.C. §103(a) as being obvious over Ekwuribe (U. S. Patent No, 5,359,030, hereinafter Ekwuribe '030) in view of Delgado '052 and WO 97/14740; and

claims 1-18 were rejected under 35 U.S.C. §103(a) as being obvious over Ekwuribe '030 in view of Delgado '052 and WO 97/14740 and in further view of Harris, EP o 511 903 or Lee '703.

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 1-20 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-104 of U.S. Patent No. 6,713,452; and claims 1-6 and 8-18 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-130 of U.S. Patent No. 6,770,625. Applicants have filed herewith terminal disclaimers wherein any term extending beyond the expiration of U. S. Patent Nos. 6,713,452 and 6,770,625 is disclaimed.

Claims 19-20 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of U.S. Patent No. 6,835,802 in view of Lee, et al. (U.S. Patent No. 6,506,730, hereinafter Lee '730). Applicants have cancelled claims 19-20 thereby obviating this rejection. Accordingly, applicants request the withdrawal of all rejections under judicially created doctrine of obviousness-type double patenting.

Rejection under 35 U.S.C. §103(a)

1. Claims 15-17 were rejected under 35 U.S.C. §103(a) as being obvious over EP 0 511 903 in view of Delgado '052 and WO 97/14740. Applicants submit that the proposed combination of references does not establish a *prima facie* case of obviousness.

Initially, it should be noted that claim 15, as amended herein, recites as follows:

15. A monodispersed mixture of conjugates, wherein each conjugate consists of a calcitonin coupled to at least one polyethylene glycol moiety consisting of at least 4 polyethylene glycol subunits, wherein coupling between the calcitonin and the polyethylene glycol moiety consists an amine bond(s), said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.

Thus, claim 15 recites a mixture of molecules wherein the polyethylene glycol is coupled to an amine function of the calcitonin.

EP 0 511 903 teaches the use of polydisperse oligomers for conjugation to the carboxylic group of calcitonin. Notably, it should be recognized that this untranslated reference does not teach or suggest a conjugate wherein the oligomer is coupled to an amine group of the calcitonin. As such, there is no teaching or suggestion of the conjugate of the presently claimed invention. Further, clearly there is no

teaching or suggestion of a monodispersed mixture having a molecular weight distribution that includes a standard deviation of less than 22 Daltons.

Applicants have been disadvantaged by the Office because the Office used an untranslated reference as evidence of unpatentability. This untranslated reference provides no indication of what the teachings would mean to one of ordinary skill in the art. Notably, this untranslated reference would not be sufficient evidence for the Board of Patent Appeals and Interferences to determine unpatentability because the lack of translation fails to provide an adequate understanding of the primary reference. The Office bears the burden of providing a translation to the applicants. As such, applicants request that a translation of the specification be provided so that applicants can prepare a complete response after a thorough review of the cited reference.

The Office has combined this untranslated primary reference with several secondary references. However, these secondary references do not cure the defects of the primary reference. WO 97/14740 teaches a method of synthesizing PEG molecules. However, there is no evidence in the specification whether there was production of discrete-length PEG molecules. The Examples only describe synthesis of discrete length “polyethylene glycol-containing compounds” such as the amine containing compounds in Example 1. Clearly, there is no disclosure that ensure the synthesis of polyethylene glycol moieties that do not include additional functional groups. Further, the synthesis methods provide no teachings or suggestions to provide a monodispersed mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons or a mixture that exhibits a dispersity coefficient (DC) greater than 10,000. The WO 97/14740 synthesis method is described in the examples with no discussion regarding the purity of the conjugates. Thus, the dispersity of the conjugates is unknown **and that which is unknown cannot be obvious**. Further, the Office is not allowed to speculate regarding that which is unknown.

Delgado ‘052 teaches the fractioning of different sized PEG-protein adducts by partitioning in a PEG-containing biphasic system. Importantly, there is no information regarding preferred molecular weight or length of the PEG molecule. Further, there is no discussion describing the conjugation of any size PEG molecule to **an amine function** of calcitonin. This Delgado reference only provides “estimations” and **does not in any way teach or suggest the ability to isolate a monodisperse mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons or a mixture having a dispersity coefficient (DC) greater than 10,000.** As stated in

column 8, of the cited reference, “the PEG molecules have an average molecular weight of about 5000,” but there is no discussion regarding using a monodispersed mixture or generating a mixture wherein all the molecules are essentially the same molecular weight. The biphasic separation may be able to separate different groups by the level of substitution, but this reference provides no guidance to go in the direction of applicants’ claimed invention. Notably, the only thing Delgado teaches includes the ability to show a linear relationship between the log of a determined partition coefficient of PEG proteins and the number of amino acids coupled to the PEG. However, as stated at the top of column 11, there seems to be some concern that using a partition coefficient is even sufficiently accurate to determine the number of PEG molecules attached to a protein. Further, as discussed in column 12, there is a great deal of uncertainty regarding the described method being applicable to different types of proteins because the correlation between the log of a determined partition coefficient of PEG proteins and the number of amino acids coupled to the PEG was no longer applicable. Thus, there is no motivation that this method would even be effective with calcitonin.

Notably, obviousness cannot be established by combining the teachings of the cited references to produce the claimed invention, absent some teaching or suggestion supporting the combination and suggesting the desirability of the combination. Applicants respectfully submit that the Office’s statement “that the claimed invention would be obvious to one having ordinary skill in the art” is not sufficient by itself to establish *prima facie* obviousness. According to the Board in *Ex parte Humphreys*, 24 USPQ2d 1255, 1262 (B.P.A.I. 1992) the Office was wrong in rejecting the claims for obviousness because the examiner’s rejection was not **specific** as to how one of ordinary skill in the art would have found it obvious to combine the references. Furthermore, they noted the examiner had not explained with any **specificity what areas of the references would suggest the combination**.

This is the circumstance here. The Office has not identified any objective or specific teachings or suggestion in the cited references that would motivate one skilled in the art to combine the references to provide conjugates such as recited in applicants’ claims 15-17. Thus, the Office seems to be merely picking and choosing from the cited references and reinterpreting the prior art in light of applicants’ disclosure, in order to reconstruct applicants’ claimed invention, but without any instructional or motivating basis in the references themselves. Such approach is improper and legally insufficient to establish any *prima facie* case of obviousness.

Still further, even if the references were combinable, which of course, they are not, the proposed combination would not teach or suggest each and every element of the claimed invention. For example, none of the references alone or in combination teaches or suggests conjugates consisting of a calcitonin coupled to the polyethylene glycol moiety through amine bonds of the calcitonin and having a molecular weight distribution with a standard deviation of less than about 22 Daltons or a mixture having a dispersity coefficient (DC) greater than 10,000.

In light of the above discussion and the fact that (1) there is no motivation, suggestion or teaching to combine the references; and (2) each and every element is not taught or suggested by the proposed combination, it is clear that the cited combination fails to establish a *prima facie* case of obviousness of applicants' claims as herein amended.

2. Claims 15-17 were rejected under 35 U.S.C. §103(a) as being obvious over EP 0 511 903 in view of Delgado '052 and WO 97/14740 and in further view of the Harris. This proposed combination does not defeat the patentability of the presently claimed invention.

As discussed above, the combination of EP 0 511 903, Delgado '052 and WO 97/14740 does not establish a *prima facie* case of obviousness and the addition of Harris does not overcome the shortcomings of the proposed combination.

Harris discusses the need to determine the effects of molecular weight and degree of substitution in each case. The reference clearly does not discuss using a monodispersed mixture wherein the molecules are so similar in weight that the standard deviation is less than 22 daltons or that the dispersity coefficient is greater than 10,000. As previously stated, none of the cited references describe this type of monodispersity.

The Office contends that "it would have been obvious to one having ordinary skill in the art to optimize result-effective conjugate properties in order to maximize the conjugate's desirable properties." Applicants argue that this rejection amounts to the application of an "obvious to try" standard which is known to be an improper standard for a §103 rejection. The Office contends that because the references discuss determining ideal substitution and length of PEG, there is sufficient motivation to make obvious the presently claimed invention. However, these simple statements regarding substitution and length of PEG provide little guidance regarding effective level of purity or

monodispersity. The prior art has not provided guidance as to which parameters are critical and given no direction as to which of the many choices is likely to be successful.

The Board in *Ex parte Obukowicz*, 27 USPQ2d 1063, 1065 (B.P.A.I.) (citing *In re O'Farrell*, 853 F.2d 894, 7 USPQ 2d 1673, 1681 (Fed. Cir. 1988)) addressed this very issue. In *Obukowicz* the invention concerned incorporating a DNA sequence, for a substance toxic to plant pests, directly into the genetic code of bacteria. The bacteria were then applied to plants whereon the bacteria produced and extruded the toxic substance, which in turn was consumed by the plant pests. The claimed invention was initially rejected by the examiner because a prior art reference mentioned combating mosquitoes using genetically engineered bacteria such as "natural pond microflora". However, the Board ruled that the mere mention of "natural pond microflora" was insufficient to provide the necessary suggestion or modification. As stated by the Board:

"the statement (in prior art) is but an invitation to scientists to explore a new technology that seems a promising field of experimentation. The Dean statement is of the type that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it. Such a suggestion may make an approach "obvious to try" but it does not make the invention obvious."

Applicants carefully scrutinized all the references and contend that a general statement about optimizing substitution and/or molecular weight, without any additional guidance is not sufficient to meet the Office's burden of establishing a *prima facie* case of obviousness.

3. Claims 15-18 were rejected under 35 U.S.C. §103(a) as being obvious over Ekwuribe '030 in view of Delgado '052 and WO 97/14740. Applicants submit that this proposed combination does not render the presently claimed invention as obvious.

The Office has already recognized that Ekwuribe '030 does not teach or suggest the use of a monodisperse conjugate wherein these monodispersed conjugate mixtures have low molecular weight distribution standard deviations and high dispersity coefficients. However, the Office seems to believe that either Delgado '052 or WO 97/14740 overcomes the shortcomings of Ekwuribe '030. Applicants vigorously disagree.

Initially, it should be noted that Ekwuribe '030 does not teach the conjugates of the presently claimed invention. The presently claimed conjugates consist of a calcitonin and a polyethylene glycol moiety

consisting of at least 4 polyethylene glycol subunits. These conjugates are different from that of Ekwuribe '030 because all of the molecules taught or suggested by Ekwuribe '030 comprise not only a polyethylene glycol but also a lipophilic moiety. Ekwuribe '030 teaches the importance of the lipophilic moiety at column 12, lines 53 to 62 and discusses the importance of the lipophilic portion to prevent aggregation. Importantly, Ekwuribe '030 does not teach or suggest a conjugate that does not include such a lipophilic portion. Thus, Ekwuribe '030 does not teach or suggest the claimed conjugates of the present invention.

The Office has combined Ekwuribe '030 with Delgado '052 and WO 97/14740. However, this proposed combination does not provide any guidance or motivation to go in the direction of applicants' claimed invention. As stated above, WO 97/14740 teaches and enables the production of PEG containing molecules. However, the synthesis methods provide no teaching or suggestion to provide a monodispersed mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons or the mixture that has a dispersity coefficient (DC) greater than 10,000. Further, WO 97/14740 does not teach or suggest conjugates that include a calcitonin coupled to a polyethylene glycol moiety wherein coupling consists of an amine bond(s).

Delgado '052 teaches the fractioning of different sized PEG-protein adducts by partitioning in a PEG-containing biphasic system. Importantly, there is no information regarding preferred molecular weight or length of the PEG molecule. Clearly, there is no discussion describing the conjugation of any size PEG molecule to an amine function of the calcitonin. This Delgado reference does not teach or suggest the isolation of a monodisperse mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons or a mixture having a dispersity coefficient (DC) greater than 10,000.

According to the Office:

"It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the calcitonin conjugates of Ekwuribe using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see *In re Kamlet*, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Ekwuribe; because the use of discrete length PEG in the conjugates of Ekwuribe would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by WO Patent Application '740; because purifying the

PEG conjugate according to the method of Delgado would have been expected to have the benefits of being able to isolate the specific conjugate having the most desirable biological properties.”

Applicants vigorously disagree and remind the Office that “teachings of references can be combined *only* if there is some suggestion or incentive to do so.” *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 221 USPQ 929, 933 (Fed. Cir. 1984)) (emphasis in original).

Thus, it is incumbent on the Office to provide some suggestion or teaching in the prior art that would lead one skilled in the art to proceed in the direction of applicants’ claimed invention; especially in light of the above discussion concerning the fact that Ekwuribe ‘030 conjugate must include a lipophilic moiety. Furthermore, there is no teaching or suggestion in the proposed combination that provides for a monodispersed conjugate meeting the limitations of the present claims relating to molecules that are so similar in weight that the standard deviation is less than 22 daltons or that the dispersity coefficient is greater than 10,000, especially when these limitations are not recognized in the applied references.

The mere fact that the prior art may be modified in the manner suggested by the Office does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). Despite the Office’s attempt to buttress the obvious modification rationale by relying on an unsupported assertion of common knowledge in the art, it is well settled in the law that the Office must point to some concrete evidence in the record in support of such findings. *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002). The Office has not shown such evidence and mere speculation is not sufficient to meet the requirements of establishing a *prima facie* case of obviousness.

Accordingly, applicants respectfully request that the rejection of claims 15-18, on the basis of obviousness, be withdrawn.

4. Claims 1-18 were rejected under 35 U.S.C. §103(a) as being obvious over Ekwuribe ‘030 in view of Delgado ‘052 and WO 97/14740 and in further view of Harris, EP 0 511 903 or Lee ‘703.

As stated above, the proposed combination of Ekwuribe '030, Delgado '052 and WO 97/14740 does not meet the requirements of establishing a *prima facie* case of obviousness because the proposed combination fails to teach or suggest each and every limitation of applicants' claimed invention.

Claim 1 recites as follows:

1. A mixture of conjugates, wherein each conjugate consists of a calcitonin and a polyethylene glycol moiety, wherein the polyethylene glycol moiety is coupled to an amine function of the calcitonin, wherein the mixture is a monodispersed mixture, a substantially purely monodispersed mixture or a purely monodispersed mixture.

As stated previously, Ekwuribe '030 does not teach or suggest the limitations of claim 1 and the inclusion of Delgado '052 and WO 97/14740 does not rectify the shortcoming of Ekwuribe '030. Further, the additional inclusion of Harris, EP 0 511 903 or Lee '703 still does not provide for a combination that teaches or suggests all the limitations of the presently claimed invention.

All the cited references have been previously discussed excepting Lee '703. Lee teaches the use of a PEG moiety with calcitonin. However, all of the prepared conjugates use a polydispersed PEG moiety and there is no discussion relating to the importance of monodispersity. Thus Lee '703 does not add any additional guidance above that of the other cited references. As a matter of fact, applicants question whether Lee '703 can even be combined with the teachings of Ekwuribe '030 and still maintain the operability of Ekwuribe '030. Clearly, Ekwuribe '030 requires a lipophilic moiety for effectiveness and Lee '703 does not require such a lipophilic moiety. As such, if the elements of Lee '703 are incorporated into the conjugates of Ekwuribe '030, the Ekwuribe '030 conjugates will no longer function as intended. It is well settled in the law, according to the *Gordon* Court, that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose or change its mode of operation, then there is no suggestion or motivation to make the proposed modification (See *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)).

It is evident that heretofore, no one contemplated applicants' invention because none of the cited reference provided any guidance or motivation to go in the direction of applicants' claimed invention. As stated by the Court in *In re Carroll*, 601 F.2d 1184, 202 USPQ 571, 572 (C.C.P.A. 1979) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1965)):

"One of the more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into use of hindsight.' . . . Many inventions may seem obvious to everyone after they have been made. However, 35 USC 103 instructs us to inquire into whether the claimed invention 'would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'"

The Office has attempted to pick and choose certain elements from multiple references but could not have been able to compile such a list without the help of applicants' claimed invention. This use of applicants' invention as a blueprint is unacceptable hindsight and does not provide the necessary evidence to establish obviousness.

The following table identifies the elements of applicants' claimed invention compared to those of the cited references and the results clearly show that none of the prior art alone or in combination teaches or suggests applicants' claimed invention. Thus, applicants' invention meets all requirements of patentability.

	Amine conjugation	Consisting of calcitonin and a polyethylene glycol moiety	monodispersed mixture (a)	a substantially purely monodispersed mixture (b)	a purely monodispersed mixture (c)
Present Invention	Yes	Yes	Yes	Yes	Yes
Ekwuribe 030	Yes	No	No	No	No
Delgado '052	No	No	No	No	No
WO 97/14740	No	No	No	No	No
Harris	No	No	No	No	No
EP 0 511 903	No	Yes	No	No	No
or Lee '703	Yes	Yes	No	No	No

(a) Monodispersed is used to describe a mixture of compounds wherein about 100 percent of the compounds in the mixture have the same molecular weight.

(b) Substantially purely monodispersed is used to describe a mixture of compounds wherein at least about 95 percent of the compounds in the mixture have the same molecular weight and have the same molecular structure.

(c) Purely monodispersed is used to describe a mixture of compounds wherein about 100 percent of the compounds in the mixture have the same molecular weight and have the same molecular structure.

Applicants reiterate the findings of the *Lee* Court and what is required by the Office to show a suggestion to combine references. Specifically, the *Lee* Court stated: (See *In re Lee*, 61 USPQ3d 1430, 1433 (Fed. Cir. 2002))

"The factual inquiry whether to combine references must be thorough and searching.' *Id.* It must be based on **objective evidence of record**. This precedent has been reinforced in myriad decisions, and **cannot** be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an **essential component of an obviousness holding**") (quoting *C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is **rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.**"); *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, **suggestion**, or teaching of the **desirability** of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("teachings of references can be combined *only* if there is some suggestion or incentive to do so.") (emphasis in original) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

The need for specificity pervades this authority. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected **these components for combination in the manner claimed**"); *In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination.

In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (the examiner can satisfy the burden of showing obviousness of the combination "**only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references**")." (Emphasis added)

Reading the above quote, it is apparent that the Federal Circuit in 2002 has raised the bar that the Office must meet to show a suggestion or motivation to combine references to establish a *prima facie* case of obviousness. Applicants submit that the Office has not met the current standard set forth by the Federal Circuit to show a suggestion or motivation to combine the cited references and respectfully request the withdrawal of this 103(a) rejection.

Petition for Extension of Time/Fees Payable

The applicants hereby petition for a three (3) months extension of time, extending the deadline for responding to the July 5, 2005 Office Action from October 5, 2005 to January 5, 2006. The entry of

this petition results in a petition fee of \$510.00 Further, applicants have filed herewith two (2) Terminal Disclaimers that results in a fee of \$130.00 (\$65.00 for each). A check in the amount of \$640.00 is enclosed for payment of the small entity 3-month extension fee for responding to the July 5, 2005 final Office Action and the Terminal Disclaimers. Although it is believed that no further fee is due, the Commissioner is authorized to charge any deficiencies of payment associated with Communication, or to credit any overpayment, to Deposit Account No. 13-4365.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. The pending claims, as now amended, patentably distinguish over the prior art, and in view of the forgoing remarks, it is respectfully requested that all rejections be withdrawn thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Russel is requested to contact the undersigned attorney at (919) 286-8189 to resolve same.

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Respectfully submitted,

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